Live-Attenuated and Inactivated Influenza Vaccines for Young Children (GRADE)

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Advisory Committee on Immunization Practices
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Policy Question

Should live attenuated influenza vaccine (LAIV) be recommended preferentially over inactivated influenza vaccine (IIV) for healthy children 2 through 8 years of age?

□ Rationale for selected age group:

- LAIV not licensed for children under 2 years of age
- 8 years is upper limit of age range for consideration of 1 vs. 2 doses (selected for programmatic consistency and simplicity)

□ GRADE assessment presented at February 2014 ACIP

 During discussion questions regarding use of LAIV for children with chronic medical conditions

EVIDENCE PROFILE CHILDREN WITH ASTHMA/WHEEZING

Background

□ ACIP currently does not recommend use of LAIV for children with asthma or other chromic medical conditions conferring high risk of complications or severe illness due to influenza.

□ 2013-14 Package insert for LAIV:

- "Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist Quadrivalent. FluMist Quadrivalent has not been studied in persons with severe asthma or active wheezing."
- "The safety of FluMist Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established"

Comparative Studies of LAIV and IIV Including Children with Asthma/Wheezing

Author	Season	Population	Design	Outcomes
Ashkenzi et al. PIDJ, 2006	2002-2003	6-71 months 2 RTIs in previous 12 mos.	Open-label, randomized	Medically documented wheezing Any Wheezing
Fleming et al. PIDJ, 2006	2002-2003	6-17 years clinical diagnosis of asthma plus ≥ prescription for asthm a medication within the past 12 months	Open-label, randomized	Medically attended wheezing Asthma exacerbation Asthma symptoms
Belshe et al. NEJM, 2007	2004- 2005	included children with mild or moderate asthma or wheezing history more than 42 days before enrollment.	Double-blind, placebo controlled	Medically significant Wheezing Any wheeze Hospitalization

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza Children with Asthma and/or wheezing (CRITICAL)

Studios	Studies Risk of Lance							
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% CI]	Quality	
2	Not serious	Not Serious	Not Serious	Not Serious	0.53 [0.38-0.73]	47 fewer per 1000 [27 fewer-62 fewer]	1 High	

- Culture-confirmed influenza-associated with respiratory illness
- Any strain, without regard to match
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ashkenazi 2006	14	406	22	389	24.9%	0.61 [0.32, 1.17]	-
Belshe 2007	37	572	74	573	75.1%	0.50 [0.34, 0.73]	-
Total (95% CI)		978		962	100.0%	0.53 [0.38, 0.73]	•
Total events	51		96				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 0.26$	6, df = 1 (P = 0.6	1); $I^2 = 0.9$	6	0.1 0.2 0.5 1 2 5 1
Test for overall effect:	Z = 3.85 (P = 0.0	1001)				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically significant wheezing Children with Asthma and/or wheezing (CRITICAL)

Studios	Studies Risk of							
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	0.69 [0.41-1.19]	18 fewer per 1000 [34 fewer-10 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Belshe 2007 (6-59 mos)	24	572	34	573	100.0%	0.69 [0.41, 1.19]	
Total (95% CI)		572		573	100.0%	0.69 [0.41, 1.19]	-
Total events Heterogeneity: Not applica Test for overall effect: Z = 1		18)	34			F	0.1 0.2 0.5 1 2 5 10 Favou Favors LAIV Favors IIV I

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically significant wheezing Children with Asthma and/or wheezing—no wheeze last 12 months (CRITICAL)

Studios	Studies Risk of						
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% Cl]	Quality
1	Not Serious	Not Serious	Not Serious	Serious	0.82 (0.28-2.40)	4 fewer per 1000 (17 fewer-34 more)	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	6	313	7	298	100.0%	0.82 [0.28, 2.40]	
Total (95% CI)		313		298	100.0%	0.82 [0.28, 2.40]	
Total events Heterogeneity: Not applicat Test for overall effect: Z = 0.		.71)	7				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically significant wheezing Children with Asthma and/or wheezing—wheezed in last 12 months (CRITICAL)

Studies	Risk of						
(n)	I Inconsistency I indirectness	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	0.68 [0.39-1.20]	33 fewer per 1000 [63 fewer-20 more)	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	18	259	28	275	100.0%	0.68 [0.39, 1.20]	
Total (95% CI)		259		275	100.0%	0.68 [0.39, 1.20]	◆
Total events Heterogeneity: Not applical Test for overall effect: Z = 1		.19)	28				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically significant wheezing Children with an Asthma Diagnosis (CRITICAL)

Studies	Risk of						
(n)	Bias	Inconsistency Indirectnes		Imprecision	RR[95% Cl]	Risk Difference with LAIV [95% CI]	Quality
1	Not Serious	Not Serious	Not Serious	Serious	0.74 [0.29-1.88]	20 fewer per 1000 [54 fewer-67 more]	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	7	124	10	131	100.0%	0.74 [0.29, 1.88]	
Total (95% CI)		124		131	100.0%	0.74 [0.29, 1.88]	
Total events Heterogeneity: Not applical Test for overall effect: Z = 0		.53)	10				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Studies Involving Other Chronic Conditions

HR Condition	Study	Seasons	Subjects	N	Outcomes
Cancer	ncer Carr 2008-09 Children 2011 1 season 2–21Y		28 LAIV/ 27 TIV	SAFETY (SAEs): (a) 11Yold LAIV required hospitalization for fever, cough, rhinorrhea, myalgia, mild hypertension and positive Flu A test	
					(b) 2Yold TIV developed afebrile seizure-like activity within 30 minute of TIV injection.
Cystic	Gruber 1994	1989-1992 3 seasons	Children 6M-23Y	44 LAIV / 42 TIV subject years	SAFETY: fever = no difference EFFICACY: LCI = 6 LAIV and 3 TIV
fibrosis	King 1987	1984-85 1 season	Children & young adults	27 LAIV, then MIV 1 week later	SAFETY: Reactions such as fever at Day 3 and Day 6 post-vaccination. Results not analyzed statistically.
HIV	Levin 2008	2004-05 1 season	Children 5–17Y	122 LAIV/ 121 TIV	SAFETY: SAEs based on dairy cards, phone calls &scheduled study visits on different days for each arm. "Pulmonary signs" included asthma &wheezing ≤28 days = no difference between arms.

Limitations

- Studies not powered to detect differences in wheezing/asthma outcomes among the subgroup of children with history of these conditions (wide confidence intervals).
- Data do not clearly indicate degree of asthma severity for which LAIV benefits outweigh risks.
- Relatively long follow up time (42 days)
- Few comparative data for other chronic medical conditions
- Proposed language changes for the upcoming season focus primarily on healthy children

EVIDENCE PROFILE HEALTHY CHILDREN AGED 2—8 YEARS

Outcomes

Benefits	Value	Include?	Data?
Lab-confirmed influenza	Critical	Yes	Yes
Influenza-associated mortality	Critical	Yes	No
Influenza-associated hospitalization	Critical	Yes	Yes
MAARI	Critical	Yes	Yes
ILI	Important	Yes	Yes
Influenza-associated acute otitis media	Important	Yes	Yes
Harms	Value	Include?	Data?
Medically-attended wheezing	Critical	Yes	Yes
Medically-significant wheezing	Critical	Yes	Yes
Immediate hypersensitivity/anaphylaxis	Critical	Yes	No
Febrile seizure ²	Critical	Yes	No
Guillain-Barre syndrome	Critical	Yes	No
Respiratory symptoms	Important	No	
Other neurologic outcomes	Important	No	
Fever	Important	Yes	Yes
Any related SAE ³		Yes	Yes

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza—Randomized Studies (CRITICAL)

Ctudios	Risk of					Effect		
Studies (n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% CI]	Quality	
2	Not serious	Not Serious	Not Serious	Not Serious	0.47 [0.38 – 0.58]	46 fewer per 1000 [36 – 54 fewer]	1 (High)	

- One study (Ashkenazi) was open-label
- Data from both studies restricted to children aged ≥24 m on ths (m eta-analysis by Ambrose et al, Vaccine 2012)

	Experime	ental	Conti	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ashkenazi 2006 _{(24.7}	1M) 23	790	46	819	18.8%	0.52 [0.32, 0.85]	
Dalaka 2007	. 0.4	2083	205	2083	81.2%	0.46 [0.36, 0.58]	•
Total (95% CI)		2873		2902	100.0%	0.47 [0.38, 0.58]	◆
Total events	117		251				
Heterogeneity: Tau² =	0.00; Chi²	= 0.19,	df = 1 (P	= 0.66)	; I² = 0%		0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z= 6.96 (P	< 0.00	001)				Favors LAIV Favors IIV
	Ashkenazi 2006 (24-7) Belshe 2007 (24-5) Total (95% CI) Total events Heterogeneity: Tau ² =	Study or Subgroup Events Ashkenazi 2006 (24-71M) 23 Belshe 2007 (24-59M) 94 Total (95% CI) Total events 117 Heterogeneity: Tau² = 0.00; Chi²	Ashkenazi 2006 (24-71M) 23 790 Belshe 2007 (24-59M) 94 2083 Total (95% CI) 2873 Total events 117 Heterogeneity: Tau ² = 0.00; Chi ² = 0.19,	Study or Subgroup Events Total Events Ashkenazi 2006 (24-71M) 23 790 46 Belshe 2007 (24-59M) 94 2083 205 Total (95% CI) 2873 251 Total events 117 251	Study or Subgroup Events Total Events Total Ashkenazi 2006 (24-71M) 23 790 46 819 Belshe 2007 (24-59M) 94 2083 205 2083 Total (95% CI) 2873 2902 Total events 117 251 Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66)	Study or Subgroup Events Total Events Total Weight Ashkenazi 2006 (24-71M) Belshe 2007 (24-59M) 23 94 2083 205 2083 205 2083 81.2% Total (95% CI) Total events 2873 2902 100.0% Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); l² = 0%	Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Ashkenazi 2006 (24-71M) Belshe 2007 (24-59M) 23 (24-59M) 790 (2000) 46 (2000) 819 (2000) 18.8% (2000) 0.46 (0.36, 0.58) Total (95% CI) Total events 2873 (2000) 2902 (2000) 0.47 (0.38, 0.58) Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); $ ^2 = 0.66 \rangle$; $ ^2 = 0.66 \rangle$ 12 (2000)

Evidence Profile—LAIV vs. IIV—2-8-year-olds Otitis Media—Randomized Studies (IMPORTANT)

Studies	es Risk of					∃ffect		
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Diff. with LAIV [95% CI]	Quality	
2	Not Serious	Not Serious	Not Serious	Not Serious	0.47 [0.30 – 0.73]	6 fewer per 1000 [3 – 8 fewer]	1 (High)	

		LAI\	/	IIV			Risk Ratio	Risk Ratio
ı	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ı	Ashkenazi 2006	2	1048	6	1034	7.8%	0.33 [0.07, 1.63]	
ı	Belshe 2007	26	3916	54	3936	92.2%	0.48 [0.30, 0.77]	
	Total (95% CI)		4964		4970	100.0%	0.47 [0.30, 0.73]	•
ı	Total events	28		60				
ı	Heterogeneity: Tau² =	0.00; Ch	$i^2 = 0.2^4$	1, df = 1 (P = 0.6	5); I² = 0%		0.1 0.2 0.5 1 2 5 10
	Test for overall effect:	Z= 3.31	(P = 0.0)	1009)				Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically-Significant Wheezing—Randomized Studies (CRITICAL)

Studies	udies Risk of					Effect		
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	0.87 [0.41 – 1.87]	3 fewer per 1000 [12 fewer–18 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; previously vaccinated.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	12	666	14	678	100.0%	0.87 [0.41, 1.87]	
Total (95% CI)		666		678	100.0%	0.87 [0.41, 1.87]	
Total events Heterogeneity: Not applica Test for overall effect: Z = 0		.73)	14			F	0.1 0.2 0.5 1 2 5 10 avou Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically-Significant Wheezing—Randomized Studies (CRITICAL)

Studies	ıdies Risk of							
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	1.36 [0.68 – 2.69]	3 more per 1000 [3 fewer – 16 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; NOT previously vaccinated.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	19	1521	14	1520	100.0%	1.36 [0.68, 2.69]	
Total (95% CI)		1521		1520	100.0%	1.36 [0.68, 2.69]	
Total events	19		14				
Heterogeneity: Not applical	ble						0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 0	.87 (P = 0	.38)				F	avou Favors LAIV Favors IIV

LAIV and IIV for Healthy 2 through 8 Year Olds: Evidence Table

Outcome		Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	Overall Evidence Type
	enza 2 RCT 5 OBS	Not serious Not serious	Not serious Not serious	Not serious Not serious	Not serious Serious	1 (High) 4 (V.Low)	
Hospitalization (Critical)	ical) I RCT	Not serious	Not serious	Serious	Serious	3 (Low)	2
MAARI (Critical) 1	RCT	Not serious	Not serious	Serious	Not serious	2 (Mod.)	(Mod.)
	RCT	Not serious	Not serious	Serious	Not serious	2 (Mod.)	
Otitis Media (Importa 2	ant) 2 RCT	Not serious	Not serious	Not serious	Not serious	1 (High)	
Medically Significant Wheezing (Critical) 1	t I RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	
Fever (Important) 2	2 RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	2 (Mod.)
Any Related SAE	2 RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	,

= no difference

= lower risk with LAIV

Relative Costs of LAIV and IIV

- Formal cost-effectiveness analysis not done
 - Complex due to large number of influenza products of different presentations (trivalent vs quadrivalent, prefilled syringes vs vials)
- Comparative U.S. price/dose
 - 2014-15 private sector costs (per VFC information)

Vaccine product		Price/dose
LAIV	LAIV4:	\$22.70
IV (w ith indication for ≤8 years)	IIV3:	\$7.65 -\$14.81
IN WILLING LEADIN 101 3 years)	IIV4:	\$14.90 - \$21.09

- 2008 cost effectiveness model estimated savings of \$45.80 per child with LAIV as compared with IIV
 - Unclear applicability given current range of products, including quadrivalents

2014-15 Pediatric Influenza Vaccine Price List. Available at: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html Luce BR et al, Vaccine (2008),;26:2841-2848

Considerations For Formulating Recommendations

Key Factor	Comments
Evidence type for benefits and harms	 Overall evidence Type 2 (Moderate) for efficacy and safety. Evidence lacking for some critical outcomes (influenza-related mortality, febrile seizure, Guillain-Barré syndrome, immediate hypersensitivity) Studies not powered to detect rare but serious events
Balance between benefits and harms	 Benefits outweigh harms Modestly better efficacy of LAIV (~47 fewer cases of Lab-confirmed influenza per 1000) No significant differences in rates of wheezing, fever.
Value	 Influenza Work Group placed high value on prevention of lab-confirmed influenza
Cost-effectiveness	 Uncertainty regarding cost benefit given current available range of vaccines

Limitations

- □ Published studies used trivalent vaccines (LAIV3 and IIV3)
 - All LAIV now quadrivalent; IIV3 and IIV4 both available
- □ Unclear whether greater relative efficacy is sustained with repeated vaccination/increasing age
 - Studies in adults generally have noted similar efficacy, or slightly greater efficacy of IIV

Thank You!

For more information please contact Centers for Disease Control and Prevention

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